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Regional Specificity of Sex Effects on Subcortical Volumes Across the Lifespan in Healthy Aging

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Abstract: When conceptualizing age-specific onsets and sex-specific characteristics of neuropsychiatric diseases in a neurobiological context, it may be crucially important to consider differential trajectories of aging. Here, we investigated effects of age, sex, and their interactions on absolute and relative volumes of subcortical structures with known involvement in psychiatric disorders, including the basal ganglia, thalamus, hippocampus, and amygdala. Structural MRI data of 76 healthy subjects (38 males, 19–70 years) from the ICBM database were analyzed. Age-related absolute atrophy was generally found in the basal ganglia and thalamus, while in the hippocampus decline was only observed in males, and was generally absent in the amygdala. Disproportionate degeneration in the basal ganglia and thalamus, exceeding cortical decline was specific for females. When allowing higher-order models, a quadratic model could better describe the negative relation of absolute volume and age in the basal ganglia in males, and generally in the hippocampus and amygdala. We could show that negative age-relations are highly specific for certain subcortical structures in either gender. Importantly these findings also emphasize the significant impact of analytical strategies when deciding for correction of subcortical volumes to the whole-brain decline. Specifically, in the basal ganglia disproportionate shrinkage in females was suggested by the relative analysis while absolute volume analysis rather stressed an accelerating decline in older males. Given strong involvement of the basal ganglia in both

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Wenjing Li and Marie-José van Tol contributed equally to this work.

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cognitive aging and emotional regulation, our findings may be crucial for studies investigating the onset and prevalence of dementia and depressive symptoms in male and female aging. *Hum Brain Mapp 35:238–247, 2014.*

Key words: sex differences; age effects; magnetic resonance imaging; subcortical structure; volume

INTRODUCTION

Previous postmortem and in vivo studies have consistently demonstrated that cerebral volumes of adult human brains systematically shrink with age [Courchesne et al., 2000; Gonoi et al., 2010; Good et al., 2001a; Gur et al., 1991; Jernigan et al., 2001; Pfefferbaum et al., 1994; Raz et al., 2004; Riello et al., 2005; Smith et al., 2007; Taki et al., 2011a; Xu et al., 2000], a process referred to as atrophy that has been most prominently observed in the frontal [Allen et al., 2005; Coffey et al., 1992; Jernigan et al., 2001; Raz et al., 1997] and temporal lobes [Coffey et al., 1992; Raz et al., 2005; Sowell et al., 2003]. Atrophy in these regions has been directly related to cognitive or other deficits of aging [Park and Reuter-Lorenz, 2009], but the patterns and degree of atrophy may differ between brain regions. Of note, age effects on the volume of specific subcortical brain structures with known function related to cognitive and emotional control might be even more important for understanding the effects of aging in the elderly, for example in Alzheimer's disease [Anderton, 1997; Driscoll et al., 2009] and psychiatric disorders [Bose et al., 2009; Kubota et al., 2011].

Indeed, pathology of subcortical structures such as the basal ganglia (including the caudate [Almeida et al., 2003; Harris et al., 1992; Roth et al., 2000], putamen [Harris et al., 1992; Wellington et al., 2006], and globus pallidus [Richfield and Herkenham, 1994]), thalamus [Braak and Braak, 1991; Lee and Marsden, 1994], hippocampus [Fox et al., 1996; Theodore et al., 1999], and amygdala [Braak et al., 1994; Kalus et al., 2005; Scott et al., 1991] have been related to cognitive and affective dysfunctions in degenerative neurological disorders and psychiatric disorders. However, the degree of atrophy in subcortical structures may differ between males and females [Gonoi et al., 2010; Pruessner et al., 2001; Xu et al., 2000], an observation that may be of great importance for understanding the increased vulnerability for certain psychiatric disorders and Alzheimer's disease in aging females. As of yet, a comprehensive study of the differential age trajectories in males and females of volume of the distinct subcortical structures across the lifespan is, to our knowledge, lacking.

Effects of sex on brain morphometry have been described in old age [Liu et al., 2010], in menopausal females [Goto et al., 2011a, b] and across the lifespan [Gonoi et al., 2010; Good et al., 2001a, b; Lv et al., 2010; Murphy et al., 1996; Takahashi et al., 2011; Taki et al., 2011b; Xu et al., 2000]. Moreover, strong effects of age on subcortical volumes have been reported [Walhovd et al., 2005, 2011; Ziegler et al., 2011], but only a few pioneering studies have incorporated effects of age and sex in models of subcortical atrophy. Among those studies inconsistent results were observed, which might be related to different age ranges or different methodologies. For example, utilizing manual segmentation of brain structures, Pruessner et al. [2001] reported no overall sex differences in the amygdala and hippocampus, while the hippocampus showed a significantly negative relationship between absolute volume and age in males only. However, the age range of 18–42 years may not have been ideally suited for revealing age effects, especially since it would not cover volume loss specifically related to estrogen unavailability after menopause in females [Morrison et al., 2006]. Goto et al. [2011a, b] also investigated hippocampal volume using both a VBM and atlas-based approach, and report on hippocampal decline in postmenopausal women, and hippocampal decline in males after their 60s, suggesting longer preservation of hippocampal integrity in males. Xu et al. [2000] demonstrated age-related degeneration in the left basal ganglia (i.e., across caudate nucleus, putamen, pallidum) of males but not females. Takahashi et al. [2011] studied age trajectories across the entire brain and reported on differential effects of sex in older age on relative volume of the thalamus, but divided patients in age groups (<50-years-old vs. >50-years-old), thereby missing important variance related to continuous age ranges. Importantly, none of these studies specifically tested whether the predictive value of age on volume of each subcortical structure differed between males and females.

A voxel-based morphometry study in a sufficiently robust sample did test for the formal interaction of sex and age-trajectories on whole brain gray matter, but could not observe differential age trajectories of subcortical structures in males and females [Good et al., 2001a]. However, this optimized voxel-based method may not be sensitive enough to detect differential sex effects on absolute and relative volume decreases in volume of several well defined subcortical structures, partially due to the large smoothing kernel (i.e., 12 mm full width at half maximum) necessary to overcome inaccuracies in registration performance. Also, Good et al. [2001a] restricted their analysis to age relations of relative brain volume, and could therefore not infer on the age relations of absolute volume of brain regions relative to whole brain volume. Thus, Good's study could be further amplified by using a subcortical segmentation method, that does not require spatial

smoothing and by specifically study relations of age with both absolute and relative brain volume. Additionally, further studies are needed that target the sex-specific effects on brain atrophy across the whole lifespan in subcortical regions vital for cognitive and emotional adaptation to daily life across the whole lifespan, as well as consider regional-specificity important to molecular mechanisms, for example region-specific iron deposition patterns in the basal ganglia [Aquino et al., 2009] that under the influence of hormonal regulation [Crist et al., 2009] may lead to regional specific atrophy patterns [Schuster et al., 2011].

In the current study, we thus tested for the existence of sex-related differences in age-dependent subcortical volume changes across the span of adulthood in a well-characterized sample of healthy individuals. We hypothesized that *sex* × *age* interaction effects would be specific for distinct subcortical structures, with steeper age declines in females, reflecting their increased vulnerability for cognitive and emotional disorders. Using the unbiased automated segmentation algorithm implemented in FreeSurfer, volumes of subcortical structures previously reported to show age- or sex-related variations were calculated, including the basal ganglia (caudate, putamen, and pallidum), thalamus, hippocampus, and amygdala, and relations with absolute volumes, as well as relative to global brain decline were assessed. These changes should represent sex-dependent age effects in the context of maturation, as well as whole-brain scaled volume differences and sex-specific periods of atrophy, that could explain behavioral sex-specific aspects during normal aging as well as to sex-specific vulnerabilities in degenerative pathologies.

METHODS

Subjects

A total sample of 76 healthy subjects, consisting of 38 females (age: 41.76 ± 17.08 years, range: 19–69 years) and 38 age-matched males (age: 44.32 ± 14.70 years, range: 19–70 years; $P = 0.487$) were included in the present study. Participants were selected from 86 healthy individuals (45 females/41 males, with no history of central nervous system (CNS) diseases) that were scanned by the International Consortium for Brain Mapping (ICBM), at the Montreal Neurological Institute (MNI) and were made publicly available as part of the 1000 Functional Connectomes project (http://www.nitrc.org/projects/fcon_1000) [Biswal et al., 2010]. MNI review boards approved the research protocols, and informed consent was obtained from each subject before participation. To obtain a balanced age range in both sexes, five subjects older than 70 years were excluded [including 4 females (age >78 years) and 1 male (73-years-old)], setting the upper limit to 69/70 years in females and males. We further excluded three left-handed females and one male to avoid potential confounds by different structural lateralization [Good et al., 2001b; Hamilton et al., 2007]. In addition, we discarded one MRI scan from our analyses because it lacked full brain coverage.

MRI Acquisition

All structural T1 images were obtained using a Siemens Sonata 1.5 T MR imaging system (Erlangen, Germany) with an eight-channel phased-array head coil. The scanning parameters were as follows: repetition time (TR) = 22 ms, echo time (TE) = 9.2 ms, slice thickness = 1 mm, flip angle = 30°, matrix size = 256 × 256, yielding 176 sagittal slices with in-plane resolution of 1 × 1 mm^2.

Data Preprocessing

Volumetric analysis was conducted using the FreeSurfer software package version 4.5.0 (http://surfer.nmr.mgh.harvard.edu) [Dale et al., 1999; Fischl et al., 1999]. FreeSurfer is an automated segmentation tool feasible to label brain structures and is unbiased in its segmentation processes and time-efficient as compared to manual approaches. The accuracy of FreeSurfer has been validated for relevant structures such as the hippocampus, amygdala, caudate, and thalamus [Fischl et al., 2002]. Lehmann et al. [2010] compared FreeSurfer and manual volumetric measurements, and showed that both methods were highly correlated in most regions and showed similar atrophy patterns in patient groups relative to normal controls.

The processing steps involved in the automated segmentation of brain structures have been described in detail elsewhere [Fischl et al., 2002, 2004]. In short, all T1 images first underwent intensity normalization and skull stripping. Segmentation was performed by rigid-body registration and nonlinear normalization of images to a probabilistic brain atlas, which was constructed from a manually labeled training set. Through the segmentation process, each voxel of the MRI volumes was labeled automatically as a corresponding brain region. The segmented labels were then returned to native space and the segmentation accuracy of each subcortical structure was visually inspected. Finally, volumes of the caudate, putamen, pallidum, thalamus, hippocampus, and amygdala were calculated, and the total brain volume (TBV) was measured as the summation of gray matter volumes (GMV) and white matter volumes throughout the whole brain (i.e., parenchyma), excluding the cerebrospinal fluid (CSF), ventricles, and dura mater. We chose to calculate TBV and not estimated total intracranial volume, because with aging loss of gray and white matter is substituted by CSF, and therefore total intracranial volume may not be the optimal variable to describe volumetric relations with aging. In addition, to correct for the effect of TBV the relative volume of each subcortical structure was calculated as a percentage of brain volume.

Statistical Analysis

All statistical analyses were performed using SPSS 16 (SPSS, Chicago, IL). Two linear multiple regression models

TABLE I. Volumes of total brain, gray matter, and subcortical structures in females and males

	Females ($N = 38$)		Males ($N = 38$)	
	Mean	SD	Mean	SD
Absolute volumes (mm^3)				
Total brain	1152556.71	80706.49	1294384.24	98808.60
Total GM	675838.79	40687.30	747343.71	62613.52
Caudate	7069.53	970.47	7799.74	961.73
Putamen	10269.61	1098.89	11341.05	1129.72
Pallidum	3218.95	362.41	3632.13	380.28
Thalamus	14730.68	1482.48	16321.29	1596.68
Hippocampus	8371.50	685.98	8770.39	891.50
Amygdala	2975.79	257.07	3415.61	333.82
Relative volumes (%)				
Caudate	0.6136	0.0769	0.6036	0.0679
Putamen	0.8916	0.0796	0.8771	0.0691
Pallidum	0.2792	0.0234	0.2809	0.0238
Thalamus	1.2770	0.0772	1.2619	0.0934
Hippocampus	0.7274	0.0511	0.6777	0.0463
Amygdala	0.2588	0.0217	0.2641	0.0188

SD, standard deviation; GM, gray matter; relative volume (%): (absolute volume [structure]/total brain volume) × 100.

were first set up for sex (dummy variable: females = 1; males = 0) and age separately to investigate the main effects of sex and age on all subcortical structures. Then, the interaction effects of age and sex were tested by setting up a linear general model containing an *age* term, a *sex* term, and an interaction term of *age* × *sex*. We set the significance threshold at alpha = 0.05 for the omnibus tests (multivariate main effects of age, sex, and age × sex on subcortical volumes). *Post-hoc* tests per structure were Bonferroni corrected for multiple comparisons. To optimally balance between Type-I and Type-II error, we took the correlation between the dependent variables (volumes of the six subcortical structures) into account by using the Simple Interactive Statistical Analysis Bonferroni tool (http://www.quantitativeskills.com/sisa/calculations/bonfer.htm). Using a Bonferroni correction that treats the variables as independent (proper Bonferroni: *alpha/number of tests*), would lead to a too stringent correction, as the dependent variables are not obtained in independent subgroups. Absolute volumes showed a mean correlation coefficient of $r = 0.60$, leading to an equivalent corrected *alpha* of 0.024 (number of tests = 6). Relative volumes showed a mean correlation coefficient of $r = 0.26$, and therefore a significant level of *alpha* = 0.013 is equivalent to a corrected P of <0.05. To further investigate age progression of subcortical volumes within sex, we set up a linear model with age as the predictor in females and males separately. Higher-order, i.e., quadratic models were then employed to demonstrate whether they could improve the fitness. For these follow-up analyses the above Bonferroni corrected thresholds were divided by two, as we tested for two independent samples (males and females), resulting in corrected thresholds 0.012 for absolute volumes and of 0.007 for relative volumes.

RESULTS

Total Brain and Gray Matter Volumes

Larger volumes of TBV and GMV were found in males as compared with females (Table I). TBV showed a significantly negative linear correlation with age in males ($r = -0.48$, $P = 0.002$) but not in females ($r = -0.22$, $P = 0.19$) (Fig. 1A). However, absolute GMV correlated negatively with age in both males ($r = -0.55$, $P < 0.001$) and females ($r = -0.47$, $P = 0.003$) (Fig. 1B).

Subcortical Volumes

Main effects of sex

An omnibus test showed a main effect of sex on subcortical structures ($F_{6,69} = 8.57$, $P < 0.001$, $\eta^2 = 0.43$): all the subcortical structures showed significantly smaller absolute volumes in females than in males at $P < 0.05$, Bonferroni corrected, with the exception of hippocampus ($r = -0.25$, $P = 0.03$ uncorrected) (Statistics per region are listed in Table II).

When accounting for TBV, a main effect of sex was again observed ($F_{6,69} = 5.03$, $P < 0.001$, $\eta^2 = 0.30$), resulting from a significant higher volume ratio of the hippocampus in females as compared to males (Table II). However, no significant sex effects were detected in the basal ganglia, thalamus, and amygdala.

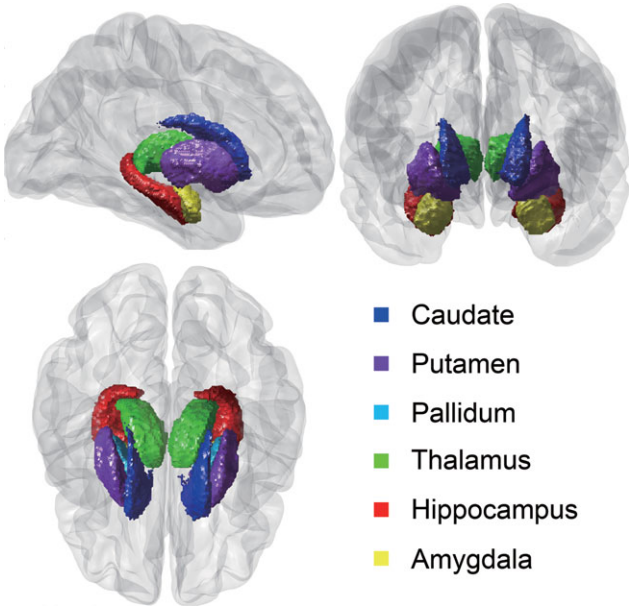

Figure 1.
3D view of subcortical segmentations. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE II. Effects of sex, age, and their interaction

	Sex		Age		Age × Sex	
	r	*P*	*r*	*P*	*F*	*P*
Absolute volumes						
Caudate	**−0.358**	**0.002**	**−0.278**	**0.015**	1.287	0.260
Putamen	**−0.438**	**<0.001**	**−0.430**	**<0.001**	0.009	0.925
Pallidum	**−0.491**	**<0.001**	**−0.335**	**0.003**	0.055	0.815
Thalamus	**−0.464**	**<0.001**	**−0.339**	**0.003**	1.786	0.186
Hippocampus	−0.246	0.032*	−0.181	0.118	**7.167**	**0.009**
Amygdala	**−0.599**	**<0.001**	−0.130	0.262	0.382	0.539
Relative volumes						
Caudate	0.069	0.551	−0.175	0.130	6.019	0.017*
Putamen	0.098	0.399	**−0.364**	**0.001**	2.464	0.121
Pallidum	−0.037	0.753	−0.271	0.018*	3.613	0.061
Thalamus	0.089	0.444	−0.272	0.018*	0.006	0.937
Hippocampus	**0.459**	**<0.001**	0.052	0.655	3.381	0.070
Amygdala	−0.132	0.257	0.065	0.578	0.720	0.399

Positive/negative *r* values for main sex effects represented larger/smaller volumes in females relative to males; in bold font: $P < 0.05$, Bonferroni corrected [with thresholds of 0.024 for absolute volumes and 0.013 for relative volumes]).
*Marginal significance ($P < 0.05$ uncorrected).

Main effects of age

A main effect of age on subcortical volumes was observed ($F_{6,69} = 3.97$, $P = 0.002$, $\eta^2 = 0.26$), resulting from significant negative linear correlations with age for absolute volumes of the basal ganglia, but not the medial temporal structures (i.e., hippocampus and amygdala) (Table II).

Effects of age were also observed on relative volumes of subcortical structures ($F_{6,69} = 2.83$, $P = 0.02$, $\eta^2 = 0.20$), that resulted from significant negative linear correlations with age in the putamen, and trend-wise in the pallidum and thalamus ($P = 0.018$). The effect of age on relative volume of the caudate was not significant (Table II). Correcting for TBV did not change the age effects on the hippocampus and amygdala.

Interaction effects of age and sex

The multivariate omnibus test indicated significant *age* × *sex* interactions on absolute subcortical volumes ($F_{6,67} = 2.64$, $P = 0.02$, $\eta^2 = 0.19$), that resulted from a significant interaction of age and sex on the hippocampus, but not on other subcortical structures. Exploration of the age effects in the hippocampus within males and females separately showed a significant negative relation in males ($r = -0.45$, $P = 0.004$), but not in females ($r = 0.06$, $P = 0.736$).

When considering relative volumes, the interaction effect was also found to be significant over all subcortical structures ($F_{6,67} = 2.62$, $P = 0.02$, $\eta^2 = 0.19$), but *post-hoc* tests were found to be only moderately significant in the caudate ($P = 0.017$) and trend-wise in the pallidum ($P = 0.06$) and hippocampus ($P = 0.07$). In these structures age had a significant negative relation with relative volumes in females, while this relation was absent in males. In the hippocampus, females showed a trend-wise positive relation of relative volume and age, while no relation with age was present in males. Correlations of absolute and relative volume of each structure with age in males and females separately can be found in Table III and Figure 2.

Higher-order model

Absolute volumes of the basal ganglia structures and thalamus preferred a high-order model (i.e., a quadratic model over a linear model) in males. In females, age-related changes within these structures were best fit with a linear model (i.e., quadratic models did not explain more variance). Of note, a higher-order model was preferred in the hippocampus and amygdala in both males and females, whereas no significant fits were observed using a linear model for females in the hippocampus and for both sexes in the amygdala. However, the higher-order model did not better fit the age-related changes after correction for TBV. Results of model fitting can be found in Table IV and Figure 3. Also in Supporting Information Figure S1, age-range (19–34, 35–50, and 51–70 years) dependent sex differences are visualized.

DISCUSSION

In this study, we investigated the relations of age on subcortical structures vital for cognitive and emotional adaptation to daily life across the lifespan, while explicitly testing for differential relations in males and females. Using an automated and rater-unbiased subcortical segmentation procedure on structural MR images, we

TABLE III. Linear regression analyses of subcortical volumes with age in females and males, respectively

	Females			Males		
	r square	*r*	*P*	*r* square	*r*	*P*
Absolute volumes						
Caudate	**0.218**	**−0.467**	**0.003**	0.029	−0.171	0.305
Putamen	**0.309**	**−0.556**	**<.001**	**0.233**	**−0.483**	**0.002**
Pallidum	**0.248**	**−0.498**	**0.001**	0.132	−0.363	0.025*
Thalamus	0.115	−0.340	0.037*	**0.276**	**−0.525**	**<0.001**
Hippocampus	0.003	0.057	0.736	**0.205**	**−0.453**	**0.004**
Amygdala	0.041	−0.203	0.223	0.064	−0.252	0.127
Relative volume						
Caudate	0.169	−0.411	0.010*	0.021	0.145	0.384
Putamen	**0.257**	**−0.507**	**0.001**	0.026	−0.161	0.333
Pallidum	**0.243**	**−0.493**	**0.002**	0.001	−0.029	0.864
Thalamus	0.106	−0.326	0.046*	0.047	−0.217	0.191
Hippocampus	0.083	0.289	0.078	0.020	−0.140	0.402
Amygdala	0.001	−0.031	0.855	0.029	0.169	0.309

In bold font: $P < 0.05$, Bonferroni corrected [with thresholds of 0.012 for absolute volumes and 0.007 for relative volumes])
*Marginal significance ($P < 0.05$ uncorrected).

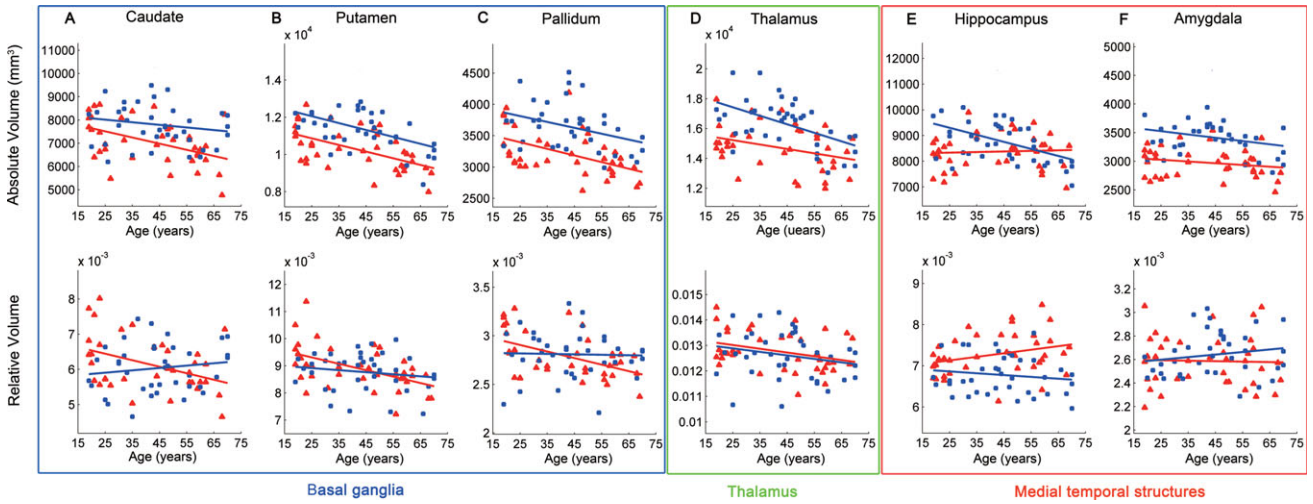

Figure 2.

Linear absolute and relative age trajectories in males and females. Linear age trajectories of subcortical volumes (including both the absolute [left column] and relative [right column] volumes) in the (**A**) caudate, (**B**) putamen, (**C**) pallidum, (**D**) thalamus, (**E**) hippocampus, and (**F**) amygdala in females (red color) and males (blue color). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

observed strong contributions of sex on absolute volume of subcortical structures, including the thalamus, caudate nucleus, pallidum, putamen, hippocampus, and amygdala, where females showed smaller volumes. Strong contributions of age where observed on basal ganglia structures and thalamus, but not on the medial temporal lobe structures. Remarkably, observed age relations depended heavily on the sex of individuals and whether volumetric decline was measured in an absolute manner or was considered relative to the whole brain age decline: An *age* × *sex* interaction effect was observed on absolute hippocampal volume: males showed a linear negative relation with age, whereas the relation was not significant in females. A second prominent observation was that in females, the basal ganglia showed a negative relation with age in volume across the lifespan, and that the pace of suggested decline

TABLE IV. The best-fitted model fitting the relationships between subcortical volumes and age in females and males, respectively

	Females			Males		
	Model	r square	*P*	Model	r square	*P*
Absolute volumes						
Caudate	**Linear**	**0.218**	**0.003**	–	–	–
Putamen	**Linear**	**0.309**	**<0.001**	**Quadratic**	**0.333**	**0.001**
Pallidum	**Linear**	**0.248**	**0.001**	**Quadratic**	**0.347**	**0.009**
Thalamus	Linear	0.115	0.037*	**Quadratic**	**0.373**	**<0.001**
Hippocampus	Quadratic	0.148	0.060	**Quadratic**	**0.321**	**<0.001**
Amygdala	Quadratic	0.137	0.075	**Quadratic**	**0.235**	**0.009**
Relative volume						
Caudate	Linear	0.169	0.010*	–	–	–
Putamen	**Linear**	**0.257**	**0.001**	–	–	–
Pallidum	**Linear**	**0.243**	**0.002**	–	–	–
Thalamus	Linear	0.106	0.046*	–	–	–
Hippocampus	Linear	0.083	0.078	–	–	–
Amygdala	–	–	–	–	–	–

In bold font: $P < 0.05$, Bonferroni corrected [with thresholds of 0.012 for absolute volumes and 0.007 for relative volumes]).
*Marginal significance ($P < 0.05$ uncorrected).
"–" indicates the relationship could not be fitted by any of the three model (linear, quadratic, and cubic models).

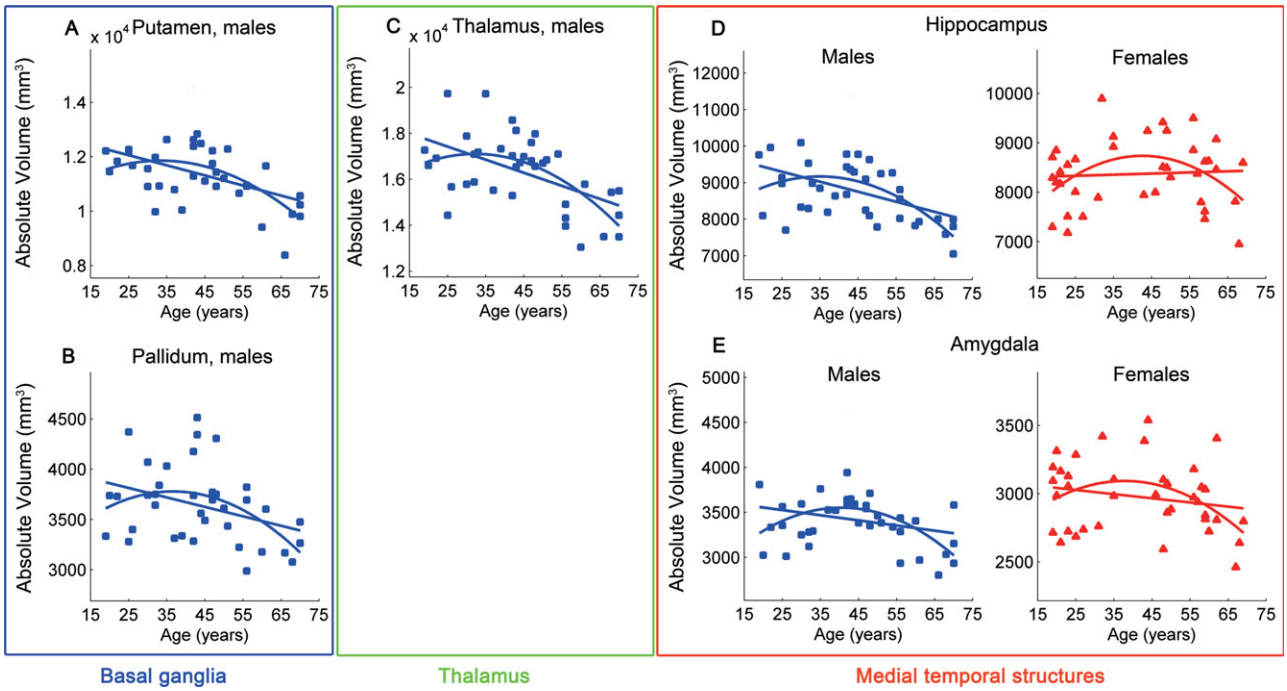

Figure 3.

Improved fitting curves of age trajectories by the quadratic model (right column) compared with the linear model (left column) in (**A**) putamen, (**B**) pallidum, (**C**) thalamus of males, (**D**) hippocampus, and (**E**) amygdala of both males (blue color) and females (red color). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

exceeded the pace of general brain atrophy (i.e., negative correlations with age after correction for TBV) and the corrected pace of suggested decline in men. In males, absolute volumes of the thalamus, hippocampus, and basal ganglia (except the caudate nuclei) showed a suggested decline, but the pace was synchronized with whole brain atrophy (i.e., no age progression beyond that of TBVs). Volume of the amygdala was shown to be absolutely and relatively preserved with age in both males and females.

Consistent with previous work that was performed on part of the current data set [Pruessner et al., 2001], we observed an absolute volume decline of the hippocampus in males, but not in females. We now extended this finding to the entire adult age range and showed a formal interaction of age and sex on absolute hippocampal volume. Previously, males have been shown to exhibit steeper negative age-related trends in the hippocampus than females, even after controlling for sex differences in body size [Raz et al., 2004]. In females, however, no decline of absolute hippocampal volumes was observed, but a weak trend towards a positive relation of relative volume and age was observed, indicating that the pace of hippocampal decline is even behind the pace of whole brain decline. Intuitively, higher-order (i.e., quadratic) models could explain the relation between age and absolute volume of the hippocampus (and amygdala) better than linear models and showed that in males (and trend-wise in females) decline of volumes was observed in the second half of life, which is consistent with a recent report [Ziegler et al., 2011]. The quadratic decline, with a suggested earlier inflection point for absolute volumes and higher absolute volumes in younger males, may support the notion that sex differences are largest at young ages (also presented in Supporting Information Fig. S1), while volumes become more similar with progressing age, consistent with Jack et al. [1998].

Within the basal ganglia—a group of nuclei (caudate, putamen, and pallidum) involved in cognitive, emotional, and motor behavior [Alexander et al., 1986], an interaction of age and sex was suggested in the caudate nucleus, and trend-wise in the pallidum, indicative of an age-progression in females in the basal ganglia beyond that of TBVs. In males age progression was either absent (caudate), or did not exceed that of general brain volumes (putamen and pallidum). Results suggest that males may exhibit more robust whole brain and parallel basal ganglia declines relative to females. The strong effect of aging on basal ganglia volumes in females may reflect common changes in functions mediated by these structures [Herrero et al., 2002], and extents the finding of Xu et al. [2000] indicating that the basal ganglia in females act as a cohesive unit subserving human behavior, when considered in their age-related changes as compared with declines in the

amygdala and hippocampus. Pronounced declines have been reported for females when compared to males in performance of a sustained reaction task and a visuospatial learning and planning task, especially at later ages [Clark et al., 2006; Proust-Lima et al., 2008]. This sex-specific effect of aging on females' psycho-motor performance would represent a suitable morphological correlate of the characteristics of female aging. In contrast, several studies did not report *age* × *sex* effects or differential aging effects on cognitive performance in males and females [Finkel et al., 2006; Kavé et al., 2012; Silver et al., 2011], which suggests that the steeper decline of the basal ganglia may be more associated with postmenopausal emotional/somatosensory abnormalities, including late-life depression, anxiety, and sleep problems. However, a direct relation of relative volumes, task performance, and emotional and somatosensory disorders needs further investigation.

In the thalamus, our results were consistent with previous studies [Van Der Werf et al., 2001], reporting that total thalamic volume reductions correlate with age in both males and females. However, further investigations of thalamic volumes should consider the numerous sub-nuclei of this structure with largely varying histo-architectonics and functions (Metzger et al., 2010). As a result of the specific involvement of individual thalamic substructures either in loops with primary sensorimotor cortices or other subcortical or frontal association areas, it is difficult to determine the contribution of general volumetric variance to a circumscribed set of psychological changes.

These considerations need to be seen in context of the intrinsic limitations of our approach. In the current study, our sample size may have been well suited for the age-related observation across the lifespan. Although the age distribution was equal over decades, only a moderate number of participants were included in each decade. However, we made optimal use of the age-variation in our sample by analyzing relations of volume of subcortical structures and age in a continuous manner. Moreover, we could replicate certain previously reported main effects of age and gender. Therefore, we are confident that our results are reliable, despite the somewhat small sample size. A second limitation is that we did not dispose of information concerning social economic status and educational level. Although we acknowledge that these factors are important when considering cognitive reserve, we aimed to only study effects of age and sex, the main predictors of regional brain volume. Thirdly, we used a cross-sectional design instead of a longitudinal design to study age-relations, which cannot fully exclude systematic e.g., cohort effects. However, observing age relations across the whole lifespan are not possible for technical reasons. We ran our study with the implicit hypothesis that such an approach would be valid, following a long line of research like many previous studies [e.g., Allen et al., 2005; Bose et al., 2009; Coffey et al., 1992; Courchesne et al., 2000; Gonoi et al., 2010; Good et al., 2001a; Goto et al., 2011a, b; Gur et al., 1991; Jernigan et al., 2001; Kubota et al., 2011; Liu et al., 2010; Pfefferbaum et al., 1994; Pruessner et al., 2001; Raz et al., 2004, 2005; Takahashi et al., 2011; Taki et al., 2011b; Walhovd et al., 2005; Xu et al., 2000; Ziegler et al., 2011]. Therefore, we feel that our approach is within an accepted line of research that is investigating age related volume changes such as decline. Finally, compared to males, females did not have such a steep decline of TBV, although their GMV significantly decreased. This might lead to a second explanation that the observed decline in females does not exceed total brain decline, but a decline in a structure when the whole brain does not show a decline in females. In our sample, whole brain volume correlated strongly to GMV ($r = 0.94$, $P < 0.001$), indicating colinearity of the two measures. This in turn suggests that the results would not change if only the GMV was considered: indeed confirmatory tests showed that using only GMV as a regressor did not change the results.

In the present study, we demonstrated that volumetric age relations depended heavily on subcortical structure and sex. Importantly, these findings also emphasize the significant impact of analytical strategies e.g., when deciding for correction of subcortical volumes to the whole-brain decline. To account for the complexity of age-related changes across the whole lifespan, we used both linear and quadratic regression models to describe the age progression of subcortical volume. This suggested an accelerating decline in old males of absolute basal ganglia volume analysis. Moreover, both absolute and relative volumes of distinct subcortical structures were studied, an approach that revealed that in females the pace of decline in the basal ganglia and thalamus exceeds the pace of general brain atrophy. This observation seems to parallel the observed neuropsychiatric vulnerability especially in aging females while atrophy in males in these structures seemed to follow rather global declines. The finding of an age × region × sex interaction on individual subcortical structures provides support for the impact of sex on psychopathologies related to reduced cognitive reserve [Perneczky et al., 2007] or depressive comorbidities [Bogerts, 2010], especially in degenerative brain disorders in the elderly. However, we further demonstrated that sex effects are highly depending on data treatment, since basal ganglia age trajectories show a highly sex dependent relative evolution against TBV, which may also explain diverging findings in the existing literature.

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